R E M A R K S

Submitted herewith is a copy of a very recent article of Brendan A. Larder, Graham Darby and Douglas D. Richman, "HIV With Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy", Science, 243, 1731-1734, March 31, 1989.

The enclosed article demonstrates that whereas isolates from AIDS patients were resistant to AZT, no such resistance was observed for the compound recited in the claims of the subject application, namely 2',3'-dideoxy-2',3'-didehydrothymidine ("D4T"). In other words, the isolates displayed sensitivities to D4T.

The results in the paper are remarkable in that the drug currently used to treat AIDS patients has been shown to be less effective than the compound recited in appellants' claims.

Respectfully submitted,

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The present invention is directed to the treatment of retroviruses such as murine leukemia virus (claim 2) and HTLV III/LAV (claim 3) (see page 5, lines 7-8 of the specification).

Claim 11 is directed to the treatment of human blood cells infected with HIV comprising administering to the cells an anti-retroviral effective amount of 3'-deoxythymidine-2'-ene (see pages 12-13 of the application).

THE CLAIMS ON APPEAL

The claims on appeal are set forth in Appendix A, attached hereto.

THE ISSUE

Is appellants' disclosure enabling under 35 U.S.C. 112, first paragraph such as to patentably support appellants' claims 1 to 7 and 11?

THE FINAL REJECTION

Claims 1-7 and 11 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement.

The Examiner alleged that the term "warm blood animals" is too broad. The Examiner further alleged that the specification was seen to be enabling only for "in vitro blood cells".

ARGUMENTS IN SUPPORT OF PATENTABILITY

In finding appellants' in vitro test results to be insufficient for purposes of enablement, the Examiner is calling for in vivo testing. However, there is presently no animal model available for evaluation of drug efficacy regarding treatment of AIDS. In this regard, see the following articles of record:

(1) Dessrosiers, R.C. and Letvin, N.L., Rev. Infect. Dis., 9, 438 (1987);

(2) Morrow, W.J.W. et al., J. Gen. Virol., 68, 2253 (1987); and

(3) J.N. Weber, et al, British Medical Bulletin, Vol. 44, No. 1, 20, (1988).

In view of the above, the Examiner's insistence of in vivo testing is tantamount to a requirement of in vivo testing in humans. This is a very strict and unreasonable standard for the granting of patent claims.

Of importance is that nucleoside analogs, of the type in the subject application, which are active in humans are active in vitro.

Of record is a copy of U.S. Patent 4,710,492, issued December 1, 1987 wherein the same supervisory Examiner herein allowed method claims for treating warm blooded animals for a similar drug for a similar disclosure for the same applicants. Have the standards for patentability changed since December of 1987?

References for the correlation of in vitro activity of nucleoside analgoues against human immunodeficiency virus, HIV, with clinical efficacy against AIDS have been made of record. Also described in articles made of record is in vitro activity data for a compound according to the invention called "D4T" and why this activity justified consideration of D4T as a clinical candidate for the treatment of AIDS.

The two nucleoside analogues for which clinical efficacy has been established are AZT: Fischl et al , New England Journal of Medicine, 1987, 317, 185-191 and DDC;

Yarchoan et al, Lancet, 1988, 76-81. The in vitro activity of AZT was first described by Mitsuya et al, Proceedings of the National Academy of Sciences USA, 1985, 82, 7096-7100 and that of DDC by Mitsuya and Broder, Proceedings of the National Academy of Sciences USA, 1986, 83, 1915-1922. Copies of these articles are of record. AZT has been approved for use in humans.

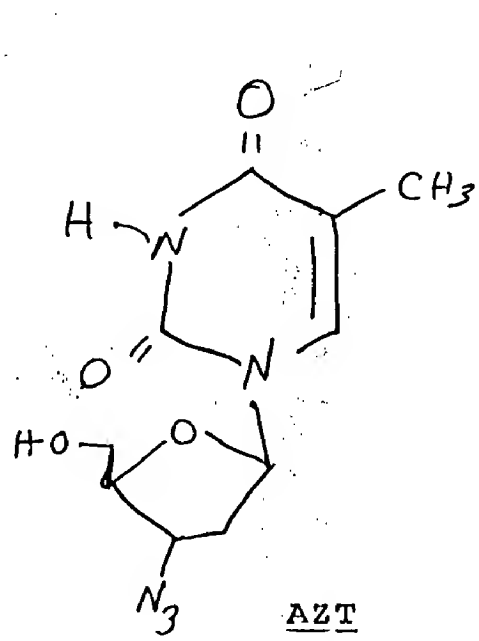
The antiretroviral activity of D4T has been published by Professor Prusoff and Dr. Lin against murine leukemia virus, Lin et al, Journal of Medicinal Chemistry, 1987, 30, 440-444, and against HIV, Lin et al, Biochemical Pharmacology, 1987, 36, 2713-2718. Copies of these articles are of record.

Also of record is the publication Herdewijn et al, Journal of Medicinal Chemistry, 1987, 30, 1270-1278, which is of interest because the authors provide in vitro results for D4T from two assay systems. In the first which utilizes ATH8 cells (Table II, p. 1273), AZT is slightly more active than D4T, but is also much more toxic; as a result, AZT has a poorer therapeutic index. DDC which inhibits the virus replication by 50% at only 0.2 micromolar is considerablly more active than either D4T or AZT. In contrast, the authors' second in vitro assay system which utilized MT4 cells (Table III, p. 1275) shows that D4T and AZT have comparable activity, and that both are considerably more potent than DDC. Because the results from different in vitro assay systems are variable, these types of experiments are use useful to identify compounds which have good potency against HIV, but are of limited utility to assign relative potency.

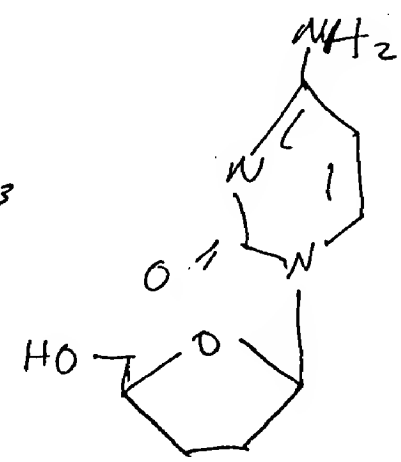
The above described Herdewijn et al paper states on page 1273 that the potency of D4T is comparable of that to AZT, but D4T is less toxic "which makes D4T a valuable candidate for further examination as a potential anti-HIV drug". They conclude this publication on page 1274 by indicating that it is "imperative to pursue"...D4T..." for more extensive pharmacological studies in the scope of developing and appropriate chemotherapy for retrovirus infections (i.e., AIDS)."

The Examiner's statement that the core structures of the nucleoside (5-halo-3'-azido-2',3'-dideoxyuridine, Yarchoan et al.) are not similar to the instant nucleoside is erroneous. This argument would lead to the rationale that the activity of 2',3'-dideoxycytidine (DDC) would probably not be active against AIDS in humans, although it was active <u>in vitro</u>. However, DDC is indeed active in humans against AIDS, although it has unpredicable toxicity.

The compound DDC is different in structure for AZT as seen below.



AZT



DDC

It is clear that DDC has no N_3, does have an NH_2 in place of O on carbon-4, and has no methyl moiety on carbon-5 of the pyrimidine moiety. Yet the two structures are similar in that they are both pyrimidine nucleosides and the parent compounds, thymidine and deoxycytidine, are natural components of viral DNA. The compounds recited in appellants' claims are also pyrimidine nucleoside analogs of thymidine and of deoxycytidine, as are AZT and DDC.

3'-Deoxythimidin-2'-ene(d4T) is similar to AZT, but lacks the N_3, and is unsaturated in the 2',3' position.

With the above in mind, reference is made to Cross v. Iizuka, 224 U.S.P.Q. 739 at 748 (Fed. Cir. 1985).

It is noted that Example 2 on pages 12-13 of the application concerns stimulated human peripheral blood mononuclear cells infected with HIV in the presence of 3-deoxythymidin-2'-ene. This example should be more than sufficient to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph. Of record is further test data - see page 2 of the April 8, 1987 Preliminary Amendment (reproduced as Appendix B herein). The Examiner has not cited any case law to support her alleged need for in vivo testing.

The Board's attention is directed to three recent Board Decisions, namely Ex parte Chwang, 231 U.S.P.Q. 751 (Bd. App. & Int. 1986) (which cited Cross v. Iizuka, 224 U.S.P.Q. 739 (Fed. Cir. 1985)), Ex parte Krepelka et al, 231 U.S.P.Q. 746 (Bd. App. & Int. 1986) and In re Hirsch, BNA PTCJ, Vol. 34, No. 850, October 8, 1987, pp. 588-589.

With regard to the Examiner's assertion that "At present, in vitro tests for AIDS virus has not been accepted as being predictive of efficacy in treating humans", the Board's attention is directed to Ex Parte Rubin, 5 USPQ 2d 1461 (Bd. App. & Int. 1987) which involved cancer treatment, the treatment of which was heretofore regarded by some patent examiners with as much or more skepticism as the treatment of AIDS is today.

The Examiner is apparently trying to limit appellants only to their working examples and this is improper.

See In re Anderson, 176 USPQ 331, 333 (CCPA 1973), where the Court held that

> " we do not regard §112, first paragraph, as requiring a specific example of everything within the scope of a broad claim...What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the disclosure of a broader invention. This it may not do."
>
> > " It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name ever such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it."

Indeed, examples per se are not required to satisfy the requirements of 35 U.S.C. 112, first paragraph. See In re Strahilevitz, 212 USPQ 561, 562-563 (CCPA 1982); In re Stephens, 188 USPQ 659, 660-662 (CCPA 1976); In re Borkowski, 57 CCPA 946, 164 USPQ 642, 645-646 (CCPA 1970); In re Gay, 50 CCPA 725, 135 USPQ 311, 316 (CCPA 1962).

The Court held in In re Robins, 166 USPQ 552, 555-556 (CCPA 1970) that working examples are only one means

of satisfying the enablement requirement of 35 U.S.C. 112, and that the mere listing of specific compounds, chemical substituents, solvents, cross-linking agents, etc. in the specification would in most cases provide suitable evidence of enablement equivalent to specific working examples utilizing each of the various components.

The disclosure as set forth by the appellants in the application must be given the presumption of correctness and operativeness by the Patent and Trademark Office. The only relevant concern of the Patent and Trademark Office is the truth of the assertions in the application. In any event, the burden is on the Patent and Trademark Office whenever a rejection is made for lack of enablement under Section 112. The Examiner must explain why she doubts the truth or accuracy of the statements in a supporting disclosure to which the Examiner objects. The Examiner must back up such assertions with acceptable evidence or reasoning which contradicts appellants' contentions. See, for example, In re Marzoocchi, 169 USPQ 367, 369-370 (CCPA 1967) and In re Bowen, 181 USPQ 48, 50-52 (CCPA 1974).

The Examiner in the case at hand has not carried her burden of showing the appellants' specification to be untrue or inaccurate; indeed, the Examiner gave no evidence or reasoning for the rejection.

Appellants do not believe that any experimentation would be necessary for one skilled in the art to practice their described invention. Assuming arguendo that a certain, limited degree of experimentation would be required for one skilled in that art to reproduce appellants' invention, such experimentation would not deter from

appellants' satisfaction of the enablement requirement under 35 U.S.C. 112. See, for example, In re Miller, 169 USPQ 597, 602 (CCPA 1971); In re Angstadt, 190 USPQ 214, 218-219 (CCPA 1976); Ansul Company v Uniroyal, Inc., 179 USPQ 759, 763 (2d Cir. 1971), cert. denied, 172 USPQ 257 (1972); and Caldwell v. The United States, 175 USPQ 44, 47-48 (U.S. Ct. Cls. 1972).

It should be further noted that only those skilled in the art must be enabled, not the general public. In re Storrs, 114 USPQ 293, 296-297 (CCPA 1957).

CONCLUSION

Appellants submit that their specification is enabling for claims 1-7 and 11 and therefore request reversal of the rejection and allowance of the claims.

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Sprung, Horn, Kramer & Woods

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Date DECEMBER 1, 1982

APPENDIX A

THE CLAIMS ON APPEAL

1. A method for treating warm blooded animals infected with a retrovirus, the method comprising administering to the warm blooded animal an anti-retiroviral effective amount of 3'-deoxythymidin-2'-ene, either alone or in admixture with a diluent or in the form of a medicament.

2. A method according to claim 1, wherein the retrovirus is Moloney murine leukemia virus.

3. A method according to claim 1, wherein the retrovirus is HTLV III/LAV.

4. A method according to claim 1, wherein the 3'-deoxythymidine-2'-ene is administered intravenously in an amount of 0.01 to 10 mg per kg body weight per day.

5. A method according to claim 1 wherein the 3'-deoxythymidin-2'-ene is in admixture with a solid, liquid or liquified gaseous diluent to form a pharmaceutical composition.

6. A method according to claim 5, wherein the pharmaceutical composition contains 0.5 to 90% of said 3'-deoxythymidin-2'-ene.

7. A method according to claim 5, wherein the pharmaceutical composition is in the form of a sterile physiologically isotonic aqueous solution.

11. A method for treating human blood cells infected with HIV comprising administering to said cells an anti-retroviral effective amount of 3'-deoxythymidin-2'-ene either alone or in admixture with a diluent or in the form of a medicament.

Appendix B

With further regard to Example 2 in the above-identified application (see pages 12 to 13), further testing has revealed the results of the activity of 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) against the human immunodeficiency virus HIV (HTLV-III LAV) and the ED_{50} is 8.8×10^{-3} µM (ED_{50} is defined on page 14 of the application). In the patent application, the three levels of compound tested were 1, 10 and 100 µM. This was extended to lower concentrations as follows:

Concentration (µM)	Percent Inhibition
0.001	11
0.01	64
0.1	81
1.0	99
10.0	100